PB88-211735

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(U.S.) Health Effects Research Lab.
Research Triangle Park, NC

May 88

U.S. Department of Commerce
National Technical Information Service
NTIS

PB88-211735

EPA/600/D-88/091
May 1988

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by

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SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA *(Please read Instructions on the reverse before completing)*		
1. REPORT NO. EPA/600/D-88/091	2.	3. RECIPIENT'S ACCESSION NO. PB88-211735/AS
4. TITLE AND SUBTITLE RESPIRATORY TRACT DOSIMETRY OF AIR TOXICS		5. REPORT DATE May 1988
		6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) John H. Overton		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS Inhalation Toxicology Division Health Effects Research Laboratory - RTP, NC U.S. Environmental Protection Agency Research Triangle Park, NC 27711		10. PROGRAM ELEMENT NO. 11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Office of Research & Development Health Effects Research Laboratory - RTP, NC U.S. Environmental Protection Agency Research Triangle Park, NC 27711		13. TYPE OF REPORT AND PERIOD COVERED 14. SPONSORING AGENCY CODE EPA-600/11
15. SUPPLEMENTARY NOTES Published In: Proceedings of US-Dutch Expert Workshop on Air Toxics; The Netherlands May 1988		

16. ABSTRACT

The development of a PBPK for the whole body in which inhalation, exhalation, and metabolism in RT tissues can be simulated was described. As an example of the model's use, the results of several experiments in which rats and humans were exposed to styrene were simulated. The predicted results agreed with the empirical data. The present model results were also in agreement with the results of the model of Ramsey and Anderson (1984) which, unlike the present model, does not simulate inhalation and exhalation or explicitly model the URT and TB region. In addition to describing the development and simulation results of a PBPK model, a procedure was illustrated that used such models in combination with laboratory animal data to predict dose in humans.

17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
18. DISTRIBUTION STATEMENT RELEASE TO PUBLIC	19. SECURITY CLASS *(This Report)* UNCLASSIFIED 20. SECURITY CLASS *(This page)* UNCLASSIFIED	21. NO. OF PAGES 16 22. PRICE A03 12.95

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

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RESPIRATORY TRACT DOSIMETRY MODELING OF AIR TOXICS

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INTRODUCTION

Presented is a description of the work at the USEPA's Health Effects Research Laboratory (HERL) on the development of physiologically-based pharmacokinetic models (PBPK models) for the whole body. In general, these mathematically based models are designed to predict the dose of an inhaled, ingested, or absorbed compound at specific sites or locations in the body of humans and laboratory animals. A major reason for developing these models is that they are an integral component of the process of the quantitative extrapolation of health effects from laboratory animals to man.

Although whole body dosimetry models are being developed, our main interest is the respiratory tract (RT), the major port of entry of gases. Here, an inspired gas can react with RT tissue, causing damage, or creating toxic products that, along with the inhaled gas, are passed out of the lung to other organs. The RT also influences the rate of passage of gases or products to the rest of the body. Even though the RT is the major focus of our effort, the rest of the body cannot be neglected. Many of the air toxics are highly soluble and are transported out of the RT to other organs where they may be metabolized. The products, as well as the air toxic itself, can be circulated and recirculated to the RT via blood flow, affecting RT dose. Thus, our models must include the effects of the whole body on the transport and fate of the inhaled gases.

The modeling program for the air toxics at the HERL has two approaches that depend on the degree of complexity or sophistication of the respiratory tract (RT) part of the whole body model. One approach involves the use of highly detailed morphological descriptions of the RT combined with complex transport and chemical processes. The second approach assumes simpler RT structures and physiological processes.

There are several reasons for developing a relatively sophisticated model for RT uptake: (1) the frequency of occurrence of different cell types depends on location within the RT; (2) if there were large distal gradients of inhaled gases, then different doses in different generations could result, causing the same cell type to be at different risks to damage depending on RT location; and (3) different cell types may metabolize differently. Accounting for these factors could be important to understanding health effects in the RT.

The reasons for developing the simpler RT model include: (1) there are fewer unknown or estimated parameters than in the complex version; (2) the simulation of long time experiments is feasible because computer execution time is very much faster than for the more sophisticated model; and (3) animal variability may be such that the complex formulation cannot be verified by experimental data.

Because of space limitations and the fact that the more sophisticated model is only partially developed, only the simpler model will be discussed in detail. However for completeness, a brief discussion of the complex model is presented. Following this is a more detailed discussion of the simpler model including illustrations of simulation results using styrene as an example. The reasons for choosing styrene include the fact that experimental data as well as the results of a theoretical model (Ramsey and Andersen, 1984) are available for comparison. Furthermore, the results of the work of Ramsey and Andersen illustrate a process of extrapolating dose from laboratory animals to man, which will be discussed.

THE MODELS

Complex Model

A whole body dosimetry model for the uptake of air toxics is in the process of being developed in which USEPA's ozone (O_3) dosimetry model (Miller et al., 1985) is the basis for the RT. The RT model was developed to simulate the uptake of O_3 at the generation level in the RT of mammals. The O_3 model takes into account inhalation and exhalation, convection, molecular diffusion, dispersion, solubility, first order chemical reactions and transport in the liquids and tissues of the RT, and RT anatomy through the use of anatomical models (e.g., Weibel, 1963). As such, this model has provided a convenient starting point for the development of a whole body PBPK model that includes complex RT morphological features, and complex transport and chemical processes.

At the present stage of development, the RT dosimetry model simulates the uptake of gases that have an irreversible first order reaction with RT fluids and tissues, that are removed from the the RT by perfusion, and that are not re-circulated back to the RT. In addition, the model allows for specification, at the generation level, of groups of different cell types by characterizing the groups' physical dimensions and chemical properties and the chemical and transport properties of the inhaled gas absorbed by the cells within the group. Further development of this model to include non-linear reactions (e.g., Michaelis-Menten type metabolism) in RT tissues and fluids and non-RT compartments will depend on need and feasibility.

Simple Model Formulation

Using Ramsey and Andersen as a guide, the basic approach to developing the PBPK model was to divide the body into physiological groups which can exchange gases or compounds via blood or air flow. Each group

or RT region (which is a group) is composed of one or more compartments each of which represents similar types of body tissues, fluids, or spaces. Within each group, the concentrations of chemical compounds (in each of the group's compartments) are assumed to be in equilibrium and well mixed. However, concentrations are not in general in equilibrium between groups. It is this disequilibrium that results in the time dependence of the concentrations in the different groups.

The whole body PBPK model with the simpler RT is diagrammed in Figure 1. The RT is divided into three groups, which are chosen to correspond to the upper respiratory tract (URT), the tracheobronchial (TB) region, and the pulmonary region. Associated with each region or group is an air compartment, a blood compartment, and two tissue compartments within which metabolism can be simulated.

The simulation of inhalation and exhalation is a feature not usually found in PBPK models. This is probably because RT groups are in general not the main interest and because the effect on non-RT groups by near periodic breathing is assumed insignificant, an assumption supported by the results of successful PBPK models that do not explicitly account for inhalation and exhalation. The reasons we have chosen to simulate this process is our interest in the RT and to determine if explicit modeling of the breathing process is necessary by exploring its effects on dose in RT tissues and fluids, especially effects on non-linear metabolism in RT tissues.

That part of the whole body model which is exterior to the respiratory tract (Figure 1) is based on the model of Ramsey and Andersen (1984) for styrene. Presently, our model has four non-RT groups, liver tissue in which metabolism can occur, fatty tissue, muscle or lean tissue, and richly perfused tissue. However, this model can be expanded to allow for non-RT portals of entry as well as other physiological groups and/or compartments and an increase in the number of metabolism paths.

The time dependence of the mass or concentration in each group or compartment is expressed in terms of mass balance equations. Because the concentrations in each compartment within a group are related by partition coefficients, the mass in the group can be expressed in terms of one compartment's concentration. For example, the mass in the tracheobronchial region or group, MTB, is the sum of the mass in each compartment of the TB group and is expressed in terms of the exiting venous blood concentration, CTBV, as

$$(1) \quad MTB = (VTB/PN + VTBT1*PTBT1 + VTBT2*PTBT2 + VTBV)*CTBV,$$

where PN, PTBT1 and PTBT2 are the partition coefficients for blood to air, and for tissue to blood for the two tissue compartments, respectively. VTB, VTBT1, VTBT2, and VTBV are the volumes of the TB airspace, the two tissue compartments and the TB capillaries. Similar relationships exist for each group.

Except for the pulmonary region all volumes are assumed constant. In this region the airspace volume, VP, expands and contracts during inhalation and exhalation, respectively.

For each non-pulmonary group the time rate change of the mass of compound in the group is expressed as,

$$(2)\quad \frac{dM_g}{dt} = Q_g(CA - CV_g) + R_g + F_g,$$

where g is the group index and stands for the URT (U), the TB region (TB), the fatty (F), muscle (M), richly perfused (R), and liver (L) tissue groups, respectively. M_g is the mass of the compound in the group; Q_g is the blood flow rate through the group; CA is the concentration in the arterial blood exiting the pulmonary group and entering the group; CV_g is the concentration in the blood leaving the group; and R_g is the rate of loss due to chemical reactions. If the group is one of the RT groups then F_g is the rate of inhalation or exhalation of the gas; otherwise F_g is zero.

For the pulmonary group the mass balance equation is,

$$(3)\quad \frac{dMP}{dt} = QA(CV - CA) + RP + FP,$$

where MP is the mass in the pulmonary region; CV is the concentration in the venous blood entering the pulmonary group; QA is the blood flow rate through the pulmonary region; RP represents chemical reaction rates; and FP the rate of inhaling or exhaling the gas. The venous blood concentration, CV, is defined as

$$(4)\quad CV = \sum_g Q_g * CV_g/QA.$$

The airflow rate due to breathing is assumed to have the form of a square wave with equal inhalation and exhalation times. The expressions for the gas flow rate, F_g, for each RT airspace are similar. As an example, the TB gas flow rate for inhalation is

$$(5)\quad FTB = 2\dot{V}_E\ (CU - CTB).$$

For exhalation the rate is,

$$(6)\quad FTB = 2\dot{V}_E\ (CP - CTB).$$

In Equations (5) and (6), $\dot{V}_E$ is the minute volume; CU is the concentration in the URT airspace; CP is the airspace concentration in the pulmonary region; and CTB is the concentration in the TB region airspace.

Chemical reaction rates, R_{gj}, within each compartment j of group g are of the form,

$$(7)\quad R_{gj} = KF_{gj}*V_{gj}*CB + VMAX_{gj}*CB\ /(KM_{gj} + CB\ ).$$

The first term is a first order reaction rate with rate constant, KF_{gj}. The compartment volume is V_{gj}. The second term is a metabolism rate of the Michaelis-Menten type (Wilkinson, 1987) where $VMAX_{gj}$ is the maximum reaction rate and KM_{gj} is the Michaelis constant. CB is the blood concentration, CV_g or CA. This simple expression for rate has been found to approximate satisfactorily many metabolism rates. The total rate for each group, R_g, is the sum of the groups' compartment rates.

SIMULATION RESULTS

In order to solve the equations outlined above, values for the physiological parameters must be available. The values used for simulating the uptake of styrene are given in Table 1. Styrene is considered to metabolize effectively only in the liver; thus, metabolism is considered only in this tissue group and the values of the RT tissue and blood compartment volumes and their associated metabolism parameters have the value of zero. All parameter values, except for the air space volumes of the RT, the breathing frequency, and the tidal volumes are taken from Table 2 of Ramsey and Andersen (1984). The breathing frequency and tidal volumes are chosen so that, in conjunction with the dead space volume (URT plus TB volume), they give the same values of alveolar ventilation as used by Ramsey and Andersen (1984).

Figure 2 illustrates the effect of the simulated breathing cycle on styrene concentration in two physiological groups, pulmonary and liver. Plotted are the simulated pulmonary air and liver blood concentrations in rats for the first four seconds after being exposed to 80 ppm styrene. The concentrations in the airspace of the pulmonary region dramatically show the effect of the breathing cycle with widely varying and nearly periodic values. In contrast, the liver blood concentrations increase monotonically, with a suggestion of plateaus during time periods closely associated with exhalation times. As time increases, the periodic variations in concentrations in all the groups of the body will become less, but will not necessarily disappear, as the concentrations approach dynamic equilibrium.

Figure 3 shows plots of experimental (open symbols)and theoretical (closed symbols and solid lines) data for the concentration of styrene in the fatty tissue and alveolar blood of rats exposed for six hours to 80 ppm styrene and for 18 hours after removal from the exposure. The solid lines are moving averages over time equivalent to one breath of the results of simulations using the present model. The simulation results of this model and the results of the model of Ramsey and Andersen (closed symbols) are essentially the same; they also agree well with the experimental data presented by Ramsey and Andersen (1984).

One of the reasons the predictions of Ramsey and Andersen (1984) agree so well with the experimental data is that they chose the values of the metabolism parameters, VMAX and KM, and several other physiological parameters to obtain good agreement. The first six hours of the plotted experimental data along with the first six hours of three other experiments with styrene concentrations of 200, 600, and 1200 ppm were

used estimate the parameters. Care was taken to ensure that the values of the parameters were physiologically reasonable. Thus, one set of physiological parameters was obtained by fitting the model simultaneously to data from four experiments. A significance of this procedure is that it was part of a process that allowed these authors to accurately predict measured styrene concentrations in man. The following text and the next figure illustrates this.

In order to simulate the results of human exposure to styrene Ramsey and Andersen estimated values of the physiological parameters for man. They assumed KM to be the same as for the rat and that VMAX scaled in the same way as basal metabolism, the 0.7 power of body weight ratios. Tissue volumes were scaled from the rat volumes assuming proportionality to body weight; blood flow to each group was assumed to be in the same proportion as in the rat. These authors also assumed that the human tissue to blood partition coefficients were the same as in the rat; whereas, published data on the human blood to air partition coefficient were used. The values they assigned to the physiological parameters, shown in Table 1, were also used in the present model.

Figure 4 presents plots of styrene concentration in human alveolar blood and exhaled air as a function of time. The subjects were exposed to 80 ppm styrene for six hours. Concentrations were measured during this time and for 42 hours after exposure; however, we present the experimental data, the predictions of Ramsey and Andersen, and the results of the present model for only the first 20 hours.

Basically the theoretical predictions (closed symbols and solid lines, Figure 4) are in agreement with the experimental results (open symbols, Figure 4); thus, demonstrating the power of the extrapolation procedure used by Ramsey and Andersen (1984). In addition, the present model gives results (solid lines) that are essentially the same as the simpler model of these authors. Further discussion of the results of Ramsey and Andersen are beyond the scope of this paper; the reader is referred to their paper.

SUMMARY

The development of a PBPK for the whole body in which inhalation, exhalation, and metabolism in RT tissues can be simulated was described. As an example of the model's use, the results of several experiments in which rats and humans were exposed to styrene were simulated. The predicted results agreed with the empirical data. The present model results were also in agreement with the results of the model of Ramsey and Andersen (1984) which, unlike the present model, does not simulate inhalation and exhalation or explicitly model the URT and TB region. In addition to describing the development and simulation results of a PBPK model, a procedure was illustrated that used such models in combination with laboratory animal data to predict dose in humans.

ACKNOWLEDGMENT

The programming assistance of Dorothy Pugh and the graphics and art work of Sharon Campfield and Andy Barnett are greatly appreciated.

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FIGURE LEGENDS

Figure 1. Schematic of the physiologically-based pharmacokinetic model that has been developed to simulate the uptake and distribution of air toxics in respiratory tract and in non-respiratory tract tissues and fluids of the whole body of rats and humans. Symbols are defined in the text.

Figure 2. Predicted styrene concentrations of liver blood (dashed line) and alveolar air (solid line) for rats exposed to 80 ppm styrene versus time for the first four seconds of exposure.

Figure 3. Theoretical and experimental styrene concentrations versus time (hours) for rat exposed to 80 ppm for six hours, followed by 14 hours of non-exposure. Open symbols are the experimental data; closed symbols are the predictions of Ramsey and Andersen (1984); solid lines represent results of the present model.

Figure 4. Theoretical and experimental styrene concentrations versus time (hours) for man exposed to 80 ppm for six hours, followed by 14 hours of non-exposure. Open symbols are the experimental data; closed symbols are the predictions of Ramsey and Andersen (1984); solid lines represent results of the present model.

TABLE 1

Physiological and Biochemical Parameters For Styrene

		Rat	Human
Body weight (kg)	body wt	0.30	83.0
Alevolar ventilation (liters air/hr)	QALV	4.50	230
Tidal Volume (liters)	VT	0.002	0.5
Breaths per minute	BPM	75	13.1
Airspace volumes (liters)	VU	0.0003	.077
	VTB	0.0007	.13
	VP	0.006	3.2
Tissue group volumes (liters)	VL	0.012	3.32
	VF	0.027	7.47
	VM	0.219	60.6
	VR	0.015	4.15
Blood flow rates (liters blood/hr)	QA	5.64	290
	QL	2.11	108
	QF	0.50	26.0
	QM	0.68	34.0
	QR	2.35	121
Blood: air partition coefficient	PN	40	52
Tissue: blood partition coefficients	PL	2.7	2.7
	PF	50	50
	PM	1.0	1.0
	PR	5.7	5.7
Maximum reaction rate (mg/hr)	VMAX	3.6	184
Michaelis constant (mg/liter blood)	KM	0.36	0.36

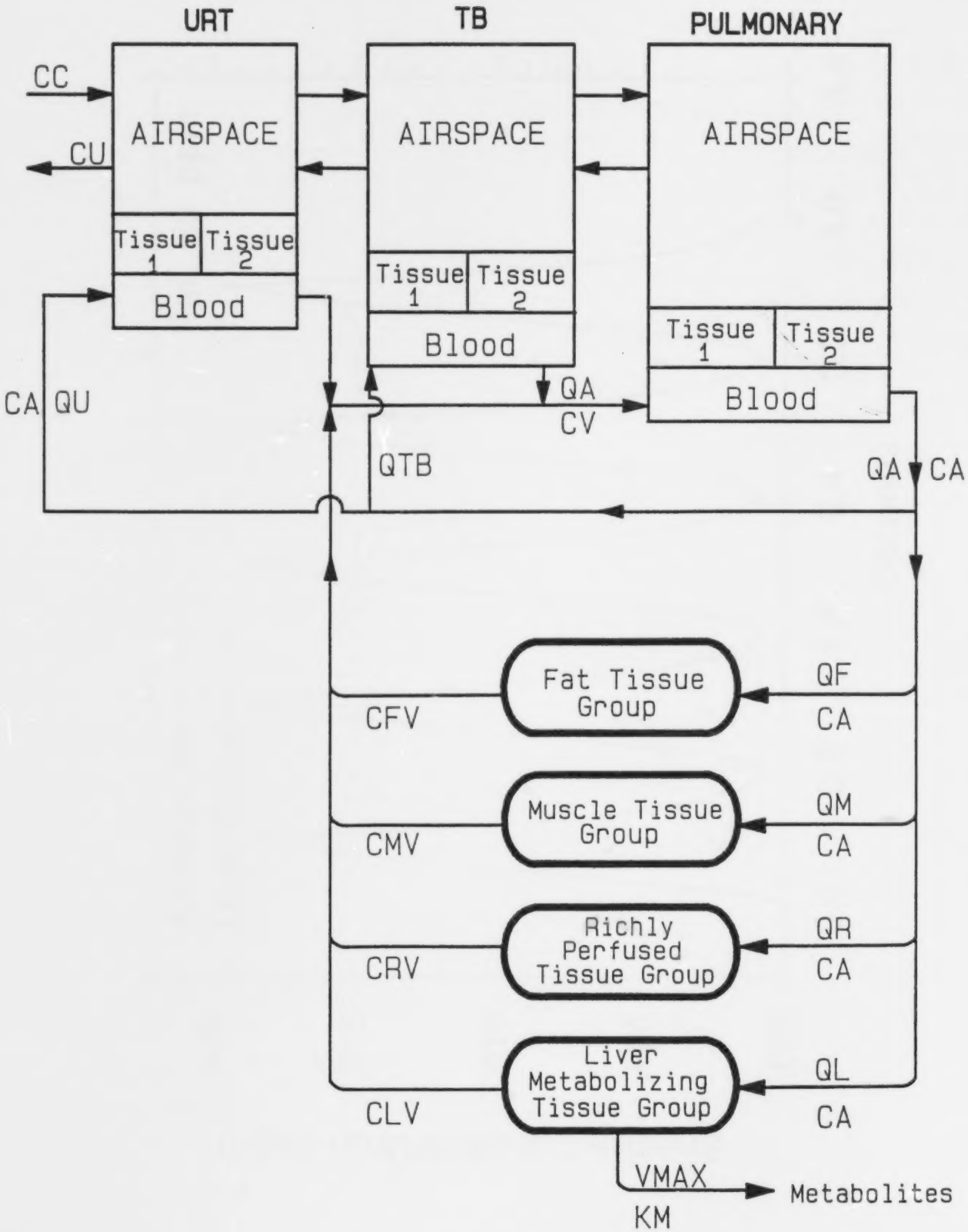
URT
TB
PULMONARY
CC
CU
AIRSPACE
AIRSPACE
AIRSPACE
Tissue 1
Tissue 2
Blood
Tissue 1
Tissue 2
Blood
Tissue 1
Tissue 2
Blood
CA
QU
QA
CV
QTB
QA
CA
Fat Tissue Group
QF
CA
CFV
Muscle Tissue Group
QM
CA
CMV
Richly Perfused Tissue Group
QR
CA
CRV
Liver Metabolizing Tissue Group
QL
CA
CLV
VMAX
KM
Metabolites

Fig 1

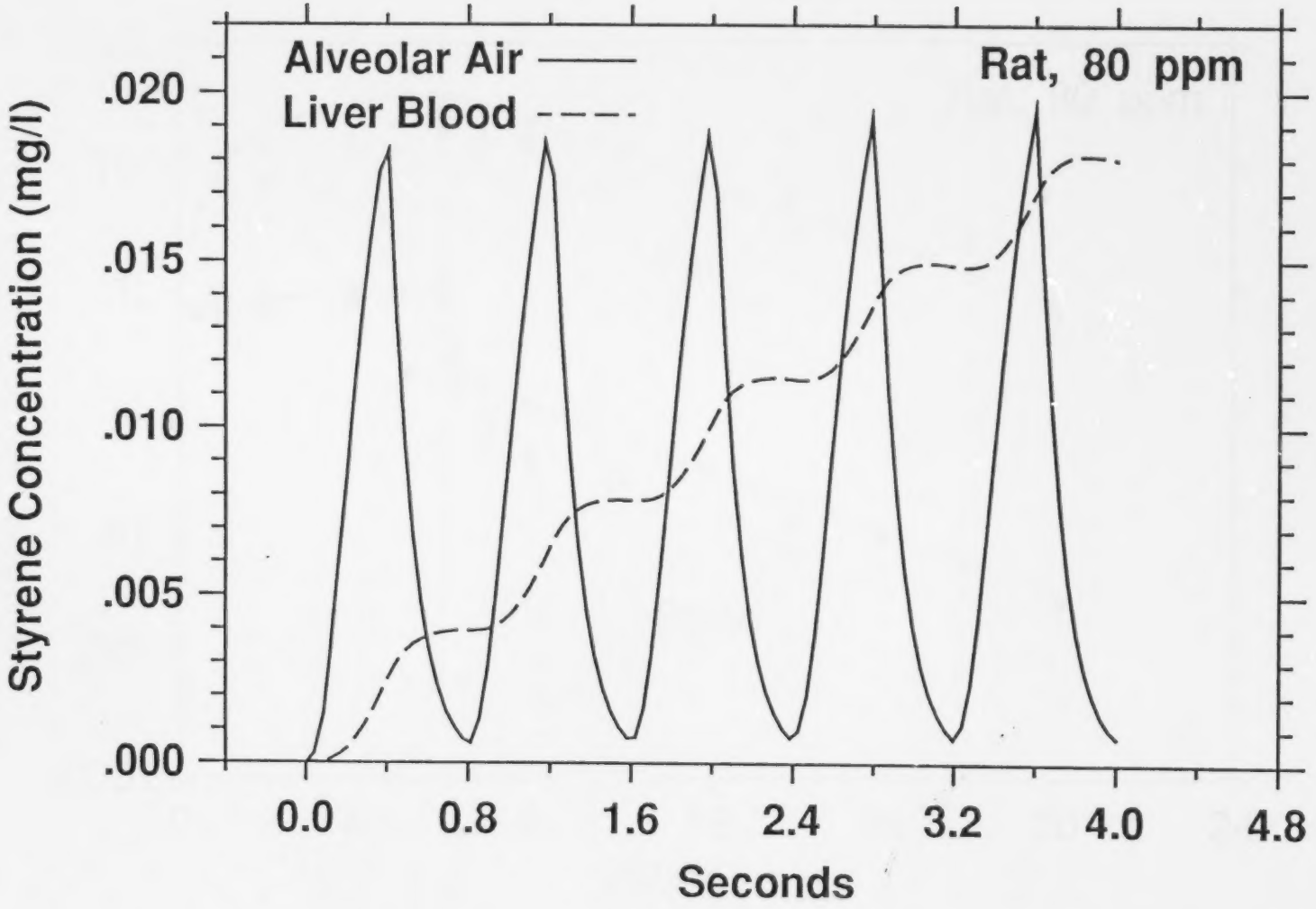
Alveolar Air
Liver Blood
Rat, 80 ppm
Styrene Concentration (mg/l)
.020
.015
.010
.005
.000
0.0
0.8
1.6
2.4
3.2
4.0
4.8
Seconds

Fig 2

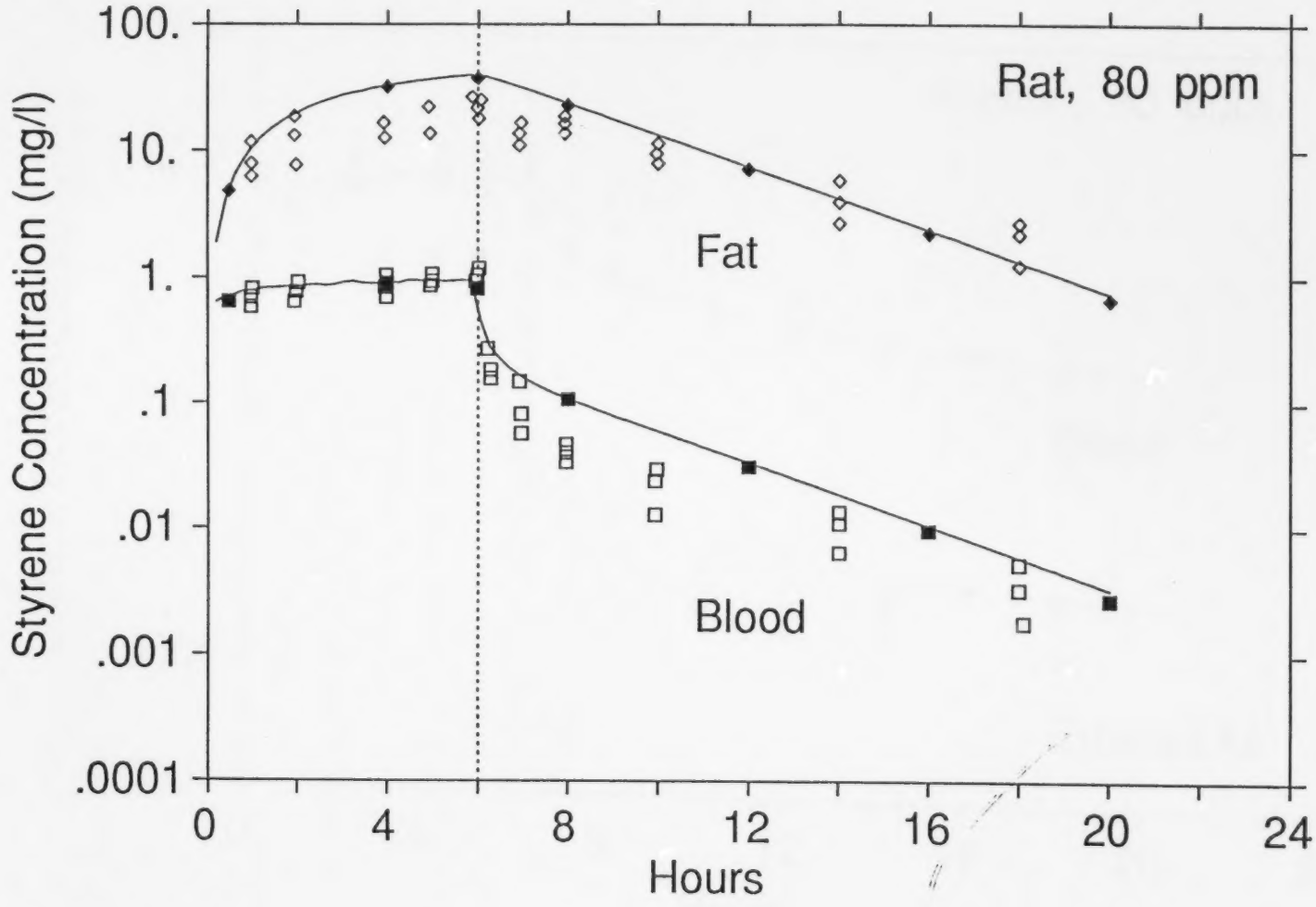
Rat, 80 ppm
Fat
Blood
Styrene Concentration (mg/l)
100.
10.
1.
.1
.01
.001
.0001
0
4
8
12
16
20
24
Hours

Fig 3

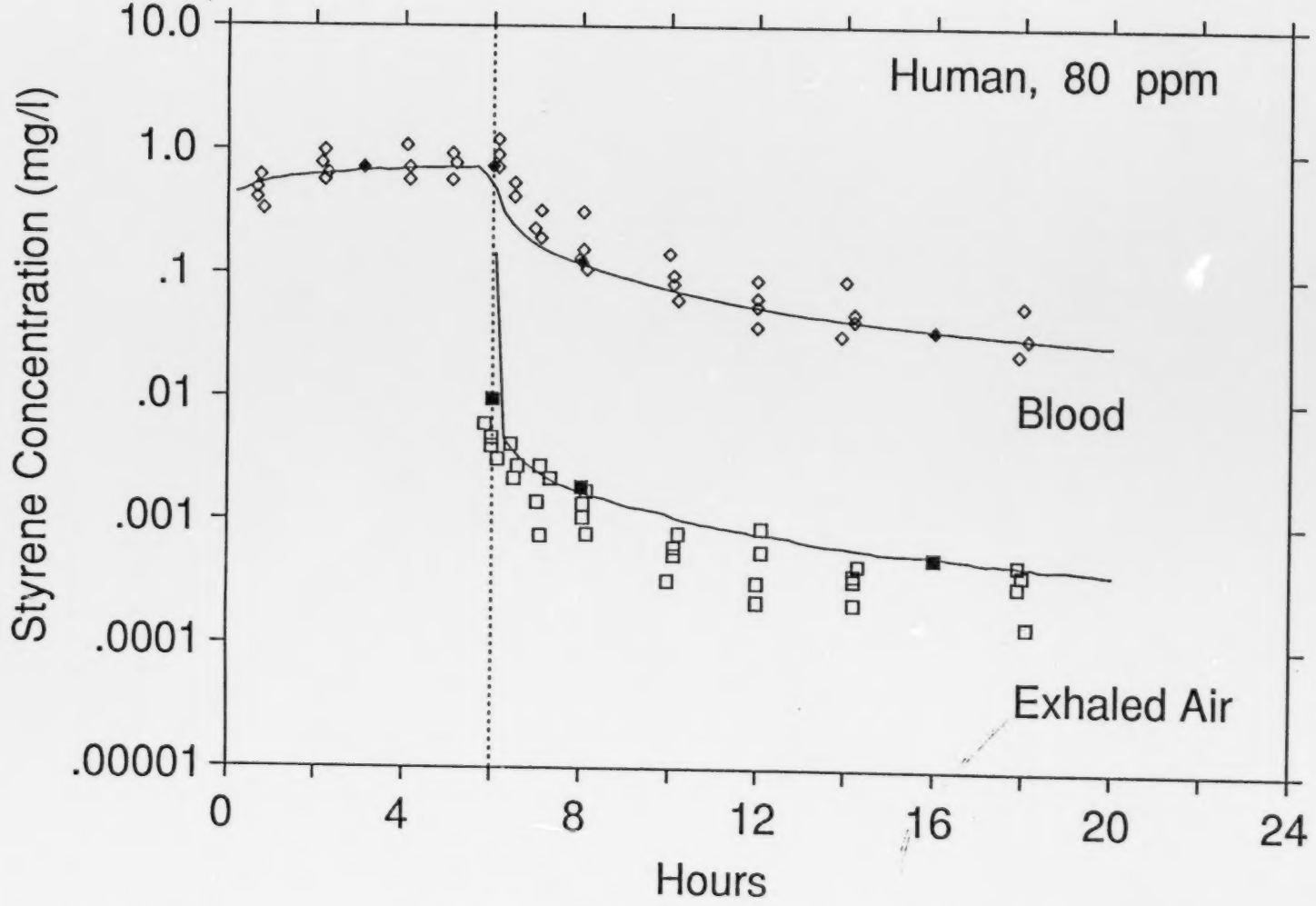
Human, 80 ppm
Blood
Exhaled Air
Styrene Concentration (mg/l)
10.0
1.0
.1
.01
.001
.0001
.00001
0
4
8
12
16
20
24
Hours

Fig 4